The Ulster Medical Journal, Volume 66, No. 2, pp. 134-135, November 1997.

Case Report

Thyroidectomy for medullary carcinoma in MEN 2A: Positive genetic screening as the sole indicator for surgery

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The multiple endocrine neoplasia type 2A syndrome (MEN 2A), comprising medullary thyroid carcinoma (MTC), phaeochromocytoma and primary hyperparathyroidism, is inherited in autosomal dominant fashion on chromosome 10. The specific genetic abnormality was initially localised to a site close to the centromere of chromosome 10[1,2] and, more recently, has been identified as a mutation (most commonly exons 10 and 11) in the RET proto-oncogene.[3] As the invariable component of MEN 2, medullary thyroid carcinoma is present in all affected individuals. Previously, the presence of tumour within a family member could only be confirmed either by the detection of clinical disease (goitre or cervical lymphadenopathy) or by the finding of elevated levels of plasma calcitonin measured basally or following stimulation with a calcitonin secretagogue such as pentagastrin or calcium. The identification of the specific genetic defect in MEN 2A now permits diagnosis of the syndrome, following routine blood sampling, in patients who may have no clinical or biochemical stigmata of disease. We record the management of a 10-year-old girl from a known MEN 2A family,[4] who underwent thyroidectomy solely on the basis of genetic information. We believe this to be the first reported occasion within the United Kingdom when a patient has undergone operation in these circumstances.

Case Report

Screening of the 10-year-old daughter of a MEN 2A family member revealed the presence of a 634 Cys-Tyr mutation within the RET gene. Her father had previously undergone total thyroidectomy for medullary carcinoma and bilateral adrenalectomy for phaeochromocytoma. Basal plasma calcitonin values at age 5, 6 and 10 years were normal. Pentagastrin stimulation testing which often results in significant retrosternal and abdominal discomfort, had not been carried out in this child. Clinical examination on each of these occasions had revealed no evidence of palpable goitre or lymphadenopathy. Urinary catecholamine levels and serum calcium were not estimated, as phaeochromocytoma and hyperparathyroidism, if present in an individual MEN 2 patient, invariably develop much later. Following appropriate discussion with parents, and solely on the basis of the genetic information, total thyroidectomy was carried out in January

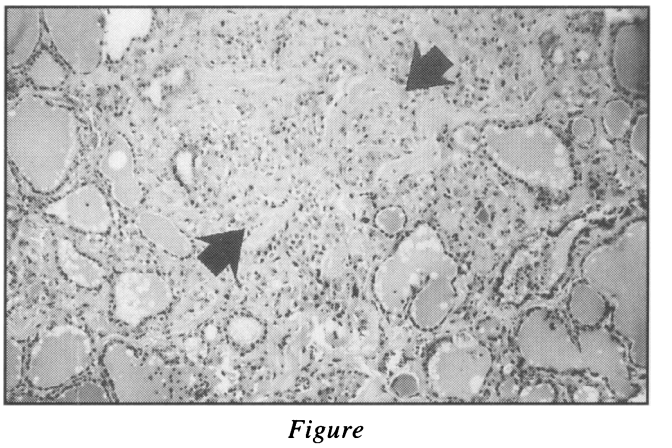

Figure
Small focus of medullary cell carcinoma infiltrating thyroid tissue. Immunocytochemistry showed tumour cells staining positively for calcitonin and CEA. H & E x 60.

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1995. At operation the thyroid gland was grossly normal. However, careful histological examination of the surgical specimen revealed the presence of C-cell hyperplasia and several small foci of frankly invasive medullary carcinoma (Fig.). The largest of these was 0.5 cm. maximum diameter. Two adjacent lymph nodes which were submitted contained no tumour. At 24-month review the patient is clinically free of disease, with unrecordable plasma calcitonin values.

DISCUSSION

Until recently, identification of affected members within MEN 2A kindreds was dependent upon the appearance of clinical or biochemical evidence of MTC after repeated and often prolonged screening. With the recognition of specific RET mutations responsible for the syndrome, its presence can now be confirmed in over 98 per cent of affected individuals following a routine blood sample. Equally important, non-affected family members can be reassured and discharged from further screening. Previously, the decision to advise thyroidectomy has usually been taken only when the plasma calcitonin level has become elevated, thus indicating the presence of MTC or its precursor, C-cell hyperplasia. Now, with the reality of a positive diagnosis made solely on genetic grounds, there is the potential for even earlier surgical intervention, with greater certainty for cure of the thyroid cancer. Following the pioneering work of Wells and colleagues[5] we advised 'prophylactic' thyroidectomy in our patient exclusively on the basis of the genetic information. The histology suggests that the operation was in fact 'therapeutic' and lends support to the belief that thyroidectomy at an even younger age may be appropriate in such circumstances.

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